activities in embryonic development and some have no role in development." Further, in the Examiner's opinion, "the particular transforming growth factors of the Akhurst abstract had been well characterized for their activity [whereas] Applicant's GDF-1 had not been."

Applicants respectfully note that, according to the Akhurst abstract submitted, the reference was published in 1990, which is the year that the earliest priority application to the present application was filed. Therefore, the Akhurst reference is an appropriate measure of what was known in the art relating to transforming growth factors at the time the present invention was made. According to the Akhurst abstract, "each" of the TGF-beta family members identified at that time played a pivotal role in embryonic processes. There is no suggestion that other TGF-beta family members known at that time played a role that did not relate to development, and the Examiner has provided no evidence to suggest that TGF-beta members known at that time were thought to "have no role in development."

Furthermore, it is Applicants' understanding upon reading the new utility guidelines (FR, Vol. 66, No. 4, January 5, 2001) that it is perfectly acceptable to assert a specific, substantial and credible utility on the basis of "homology to existing nucleic acids or proteins having an accepted utility." According to the FR Notice, a rigorous correlation is not necessary; only a "reasonable" correlation (see the FR Notice, page 1096, middle column continuing into right-hand column). As stated therein, "When a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein" (with emphasis). Id.

According to the new utility guidelines, "the asserted utility must be accepted by the examiner unless the Office has sufficient or sound reasoning to rebut such an assertion" (with

emphasis) Id. The Examiner rejects the asserted utility on the basis that the members of the TGF-beta family exhibit diverse activities, and that some members have roles not related to embryonic development. However, the Examiner provides no evidence that those of skill in the art at the time the invention was made would have believed that members of the TGF-beta super family exhibit such diverse activities as to preclude prediction of function based on this family assignment. In contrast, according to the Akhurst abstract, there had been five type beta transforming growth factors (TGF betas) identified at the priority date of the invention, each of which was found to play "a pivotal role in embryonic processes."

Thus, at the time the invention was made in 1990, one of skill in the art would have reasonably predicted that a member assigned to the TGF-B superfamily would play a role in embryonic development, and in the growth and differentiation of tissues, given that the five members identified at that time were shown to play a pivotal role in embryonic development. Indeed, according to the instant specification at page 1, "a growing number of polypeptide factors playing critical roles in regulating differentiation processes during embryogenesis [had] been found to be structurally homologous to transforming growth factor B." On that basis, and in view of the homology of GDF-1 to TGF-beta, the present inventor predicted that the GDF-1 protein was likely to play an important role in mediating developmental decisions related to cell differentiation (see page 2, lines 25-29). Moreover, it was perfectly reasonable on the basis of that prediction and the homology demonstrated according to the rules promulgated by the Office for Applicants to assert that the claimed protein would find utility in prenatal screens to detect developmental abnormalities, as disclosed on pages 12-13 of the specification.

The Examiner has provided no evidence to suggest that these predictions, which were based on the known activities of TGF-beta at the time, were unreasonable. She has presented no evidence

to back up the assertion that TGF-beta activities were thought to be so diverse at that time so as to make these predictions unreasonable. Furthermore, the argument that one could not have predicted the role of the GDF-1 protein based on homology with this superfamily should be re-evaluated in view of recent evidence with GDF-1 -/- knock-out mice that demonstrates that, in fact, Applicant's predictions were correct.

For instance, as the present inventor and others have shown in a recently published paper (Rankin et al., 2000, Regulation of left-right growth patterning in mice of growth/differentiation factor-1, Nature Genetics 24: 262-66), GDF-l plays a pivotal role in embryogenesis. A knockout mouse was generated in order to examine the biological function of GDF-1, which exhibited a spectrum of defects related to left-right axis formation in embryos, including misplacement of internal organs (Fig. 2), developmental defects in organs and cardiac abnormalities (Fig. 3). The authors concluded that these findings indicate that GDF-1 is essential for proper establishment of the left-right axis in mice, and is required for the expression of many genes expressed downstream from gdfl during development.

The Examiner dismisses the Rankin reference because it was published well after the filing date of the invention, and because knock-out mice were not routinely produced at the time of the invention. The Examiner is correct to point out that the Rankin paper was published several years after the priority date, as was she correct to note that the experiments reported in the Ebendal declaration were performed after the priority date of the invention. However, Applicants are not claiming knockout mice, nor are they claiming the methods reported in the Ebendal declaration. The Rankin reference and the Ebendal declaration were submitted to demonstrate that the GDF-1 protein has the utilities that were predicted in the specification, and are suitable as evidence for that purpose.

Thus, results with the GDF I -/- knockout mouse prove that GDF- I is required for the proper development and positioning of organs during embryogenesis. This is consistent with the function of GDF-l predicted in the specification (page 2, lines 25-29), and the results in the specification showing the expression of GDF-1 during embryogenesis (see Example 4 and Fig. 6). These results also suggest that the asserted utility of GDF1 in prenatal screens for abnormal development is a reasonable utility for the disclosed protein, given that it has now been confirmed that aberrant expression of GDF-1 has significant and substantial effects on embryonic development. A reasonable utility for the GDF- 1 protein translates to a reasonable utility for the DNA encoding that protein, as well as for vectors, host cells and methods of recombinant production.

Thus, at the time the application was filed, the TGF-beta super family was known to comprise proteins involved in embryonic development, a function that Applicants predicted that GDF-1 would share. Further, Applicants have now shown that GDF-1 does possess the predicted function, thereby supporting the disclosed utilities, i.e., use in prenatal screening for developmental defects. And as noted above, according to the new utility examination guidelines, it is perfectly acceptable to predict a specific, substantial and credible utility on the basis of homology to existing nucleic acids or proteins having an accepted utility.

The Examiner asserts that in contrast to the TGF-beta family members known at the priority date of the invention, Applicants' GDF-1 had not been well characterized with regard to activity. However, this statement seems to disregard the new utility guidelines set forth by the Office, which permit utility to be asserted on the basis of homology to existing nucleic acids or proteins having a well-established utility. As acknowledged in the Office Action, GDF-1 proteins are 26-52% similar to TGF-B family members on the amino acid level. Moreover, according to the specification at the paragraph bridging pages 19-20, GDF-1 contains all of the invariant amino acids present in the C-terminal 122 amino acids of other TGF-B superfamily members, including the seven characteristic cysteine residues as well as

many of the other most highly conserved amino acids. For instance, like the other family members, the C-terminal portion of the predicted GDF-1 polypeptide is preceded by a pair of arginine residues at positions 236-37. Thus, GDF-1 contains sufficient homology to be assigned to the TGF-beta superfamily, as substantiated by the similar assignment of other GDF proteins identified subsequently to GDF-1.

Thus, given that the new utility examination guidelines explicitly state that it is permissible to assert a credible utility on the basis of homology to a family of proteins having a well-established utility, and given that the inventors predicted and have now proven that GDF-1 would share the utility that had been well-established for members of the TGF-beta super family at the time the application was filed, Applicants respectfully request reconsideration and withdrawal of the rejections under 3 5 U. S. C. §10 1 and the enablement provision of §112, first paragraph.

Claims 3, 11-15, 22 and 24-42 were also rejected under the written description section of 35 U.S.C. § 112, first paragraph. According to the Office Action (page 6), claims 24, 25 and 35 include sequences outside the open reading frame which have not been disclosed and are therefore not described. Applicants respectfully reiterate that these claims are directed to isolated DNA segments comprising specific sequences explicitly disclosed in the specification. If the Examiner's standard was to prevail, every inventor discovering a novel DNA sequence would be limited to only that novel gene sequence, and would not be able to protect the use of that sequence once it was cloned into any vector or other larger piece of DNA. This seems unusually strict, and Applicants respectfully request consideration.

The Office Action also criticizes claim 31, which defines the claimed DNAs according to hybridization conditions, in that, Example 5 of the specification shows that even at high stringency conditions, additional bands were detected in addition to the predominant band. Applicants again respectfully submit that additional faint bands will frequently be detected in any hybridization

experiment, but the fact that a specific prominent band can be detected shows the specificity of the hybridization.

Further, Applicants had pointed out in their previous Reply that the stringency conditions noted in claim 31 (0. 1 X SSC wash) are actually considered to be high stringency conditions. For instance, as discussed in the legend to Figure 14 on page 9 of the specification, human genomic DNA probed with human GDF- I coding sequences was washed in 0.2 X SSC, whereas human genomic DNA hybridized with murine GDF-1 coding sequences was washed in 2X SSC. Thus, the conditions recited in claim 31 are suitable for identifying substantially identical sequences (as disclosed on page 10 of the specification), but a 2X SSC wash may be used to analyze cross-species hybridization. These alternative hybridization conditions are recited in new claim 39 as a means to define the claimed DNAs, and such a scope is clearly warranted in view of the experiments depicted in Figure 14.

The Office Action also maintains that no structural features were identified that could be used to define a GDF-1 protein, and the application teaches no assays for functional identification. Applicants note again that the specification discloses that the human and murine GDF-l proteins are 87% identical in the region beginning with the first conserved cysteine and extending to the C-terminus (see page 31, lines 19-20). Thus, this specific domain of GDF-1 is quite highly conserved across species, and would constitute a structural feature for identifying a GDF-l protein.

Furthermore, the instant specification does disclose an assay for identifying a GDF-1 gene, in that a probe generated from the full length murine open reading frame of GDF-1 hybridized specifically to the human gene in Southern hybridization (see Fig. 14 legend at page 9, and the relevant discussion at pages 31-32). As also shown in Figure 5, even at high stringency, a murine GDF-1 probe identified a single prominent band in both human and hamster genomic DNA. The

genomic sequences identified by these hybridization experiments could be readily cloned and sequenced using techniques that were well known at the time the application was filed.

The Office Action inquires again as to why the structure of genomic sequences should be considered to be described in the specification. Applicants respectfully submit that the pending claims, worded in terms of hybridization conditions that are clearly recited in the specification and are shown to identify the relevant sequences in the described Southern blot experiments, are clearly supported by the specification. Also, in Applicants' previous response, it was pointed out that in the past, the Examiner has cited a variety of case law for the premise that the actual DNA sequence itself must be disclosed for every sequence falling within the scope of the claims, including *University of California v. Eli Lilly,* 43 USPQ2d 1398. Applicants respectfully submit that the merits of each case must be examined on a case-by-case basis, and *Lilly* does not suggest otherwise. Moreover, *Lilly* is only relevant to the particular circumstances surrounding that case, which happened to occur at a time when the art of biotechnology was much less developed than it is now. In fact, the present application was filed after the publication of the popular Sambrook Molecular Cloning manual (2 d edition), which standardized many of the cloning procedures now used to identify and isolate genomic DNAs. Indeed, given the existence of the Sambrook manual at the time the present invention was filed, those of skill in the art would have surely seen that the inventor was in possession of the genomic DNA for the GDF- I protein upon reading the present disclosure.

For instance, in the Federal Register publication of the Written Description Guidelines for Examination (FR, Vol. 66, No. 4, page 1099, January 5, 2001), the Office answered one comment by stating that "Actual reduction to practice may be crucial in the relatively rare instances where the level of knowledge and level of skill are such that those of skill in the art cannot describe a composition structurally, or specify a process of making a composition by naming components and

combining steps" (with emphasis, see page I 10 1). In fact, the actual Guidelines state at page 1106 that:

An applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.

Footnote 42 of the Guidelines further defines some identifying characteristics for biomolecules to include sequence, structure, binding affinity, binding specificity, molecular weight, length, unique cleavage by particular enzymes, detailed restriction maps, a comparison of enzymatic activities, or antibody cross-reactivity (see page 1110 of the FR Notice). If binding specificity is one acceptable characteristic to be combined with sequence data for satisfaction of the written description requirement, then hybridization experiments showing specific hybridization with a disclosed sequence should also be sufficient.

That hybridization to a genomic sequence should be sufficient to satisfy the written description requirement is further evidenced by the fact that it was common practice at the time to isolate the genomic DNA following similar hybridizations to a genomic library. The Guidelines specify that such common techniques need not be described, because one of skill in the art would be familiar with such techniques and would incorporate such knowledge into his understanding as to what the inventor possessed at the time of filing. For instance, according to the pages from

Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual (2d edition) submitted with the previous response, libraries generated from mammalian genomic DNA had been in use since the mid-1970's for cloning mammalian genes (see page 9.2). And according to the teachings on page 9.3, it was well-known at the time this Manual was published that one could use libraries of randomly cleaved DNA to "walk" along the eukaryotic chromosome starting with a single specific probe, in order to isolate segments of DNA in and around target sequences without knowledge of the location of surrounding restriction sites.

The Examiner has responded to Applicants' arguments by noting that Applicants appear to be arguing enablement rather than written description. Applicants respectfully note that Applicants' arguments were based on the written description guidelines promulgated by the Office, and are therefore pertinent to written description of the invention. Applicants respectfully request reconsideration of the arguments as they pertain to the comments in the written description guidelines.

Thus, having full knowledge of the techniques that were well-known in the art at the time the invention was made, one of skill in the art reading the present disclosure and seeing that the disclosed coding sequences could be used as a probe to specifically identify genomic sequences by hybridization would have immediately seen that the present inventor was in possession of both coding sequence and genomic DNA comprising coding sequence. Furthermore, given the extent of homology between human and mouse GDF-1 shown in the specification, and the fact that probes generated from these sequences cross-hybridize specifically to the GDF-1 gene in alternative species using hybridization conditions specifically defined in the disclosure, it would be clear to those skilled in the art upon reading the present disclosure that Applicants were in possession of the claimed invention at the time the application was filed. In view of these remarks, reconsideration

and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, written description, is respectfully requested.

As a final matter, the Examiner has noted that page 9 does not appear to provide support for claims 39-42. Applicants apologize for any inconvenience to the Examiner, and note that the requisite support may be found on page 10, lines 8-9, where it is disclosed that 20X SSC is defined as 3M sodium chloride/0.3M sodium citrate. So, by extension, 2X SSC would be defined as stated in claim 39. Page 9, lines 11-12 give support for washing at 68°C in 2X SSC, and page 17, lines 9-13 provide support for hybridization at 65°C.

All issues raised by the Office Action dated February 11, 2002, have been addressed in this Reply. Accordingly, a Notice of Allowance is next in order. If the Examiner has any further questions or issues to raise regarding the subject application, it is respectfully requested that she contact the undersigned so that such issues may be addressed expeditiously.

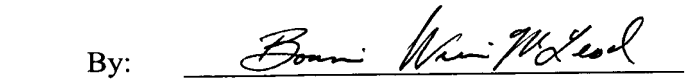
Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

Again, if the Examiner has any further questions relating to this Reply or to the application in general, she is respectfully urged to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

Dated: July 12, 2002

By: 

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